END OF LIFE CARE: PAIN MANAGEMENT

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Disclaimer

I have no financial interests or relationships with any manufacturers of products or providers of services I may reference in my presentation.

Objectives

- Discuss pain in the larger context of suffering
- Identify the differences between nociceptive and neuropathic pain
- Review pharmacological treatment strategies for nociceptive and neuropathic pain
- Discuss management of rapidly escalating pain

Chronic non-cancer pain is a separate entity from EOL pain, with different management principles and challenges.

Fast Facts and Concepts

www.capc.org

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“For Providers”

Care Settings

- Office
- Care Center/Nursing Home
- Hospital
- Hospice Room in Community Hospital
- Home

3 C's of Symptom Management

- Comfortable
- Contented
- Connected

Pain Management in Family Medicine

- Know the story
- Match pharmacology to individual need
- Titrate medication to response
- Communicate effectively
- Understand OME
- Understand opiate incomplete cross-tolerance
- Be able to recognize and reverse opiate toxicity
- Be able to manage a pain crisis

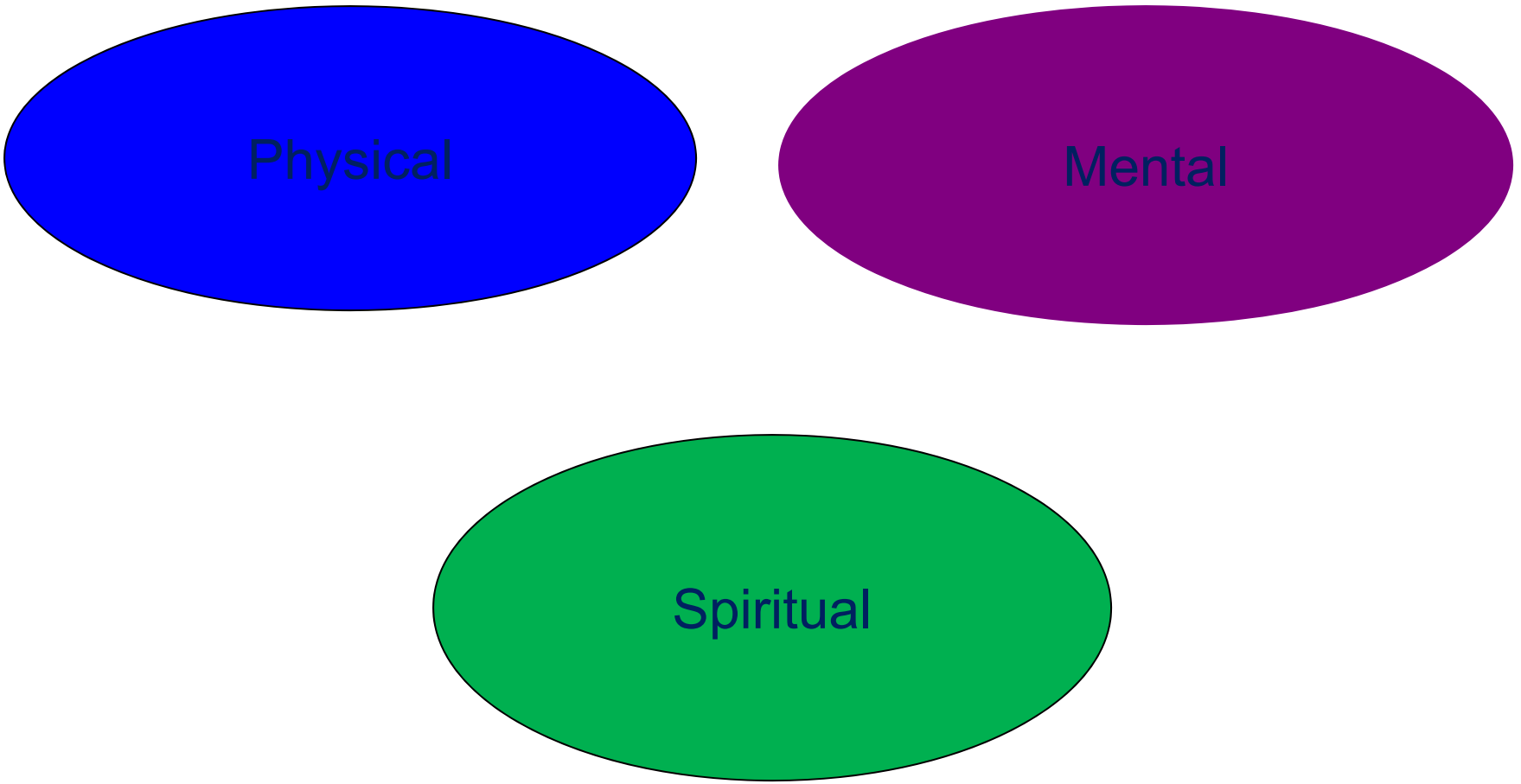
Pain Definition

"…….a somatic perception containing: (1) a bodily sensation with qualities like those reported during tissue-damaging stimulation, (2) an experienced threat associated with this sensation, and (3) a feeling of unpleasantness or other negative emotion based on this experienced threat."

Price DD. Psychological Mechanisms of Pain and Analgesia In Progress in Pain Research and Management, IASP Press, Seattle 1999. Vol 15

Total Pain

- Physical
- Emotional
- Social/relational
- Spiritual
- *Bureaucratic*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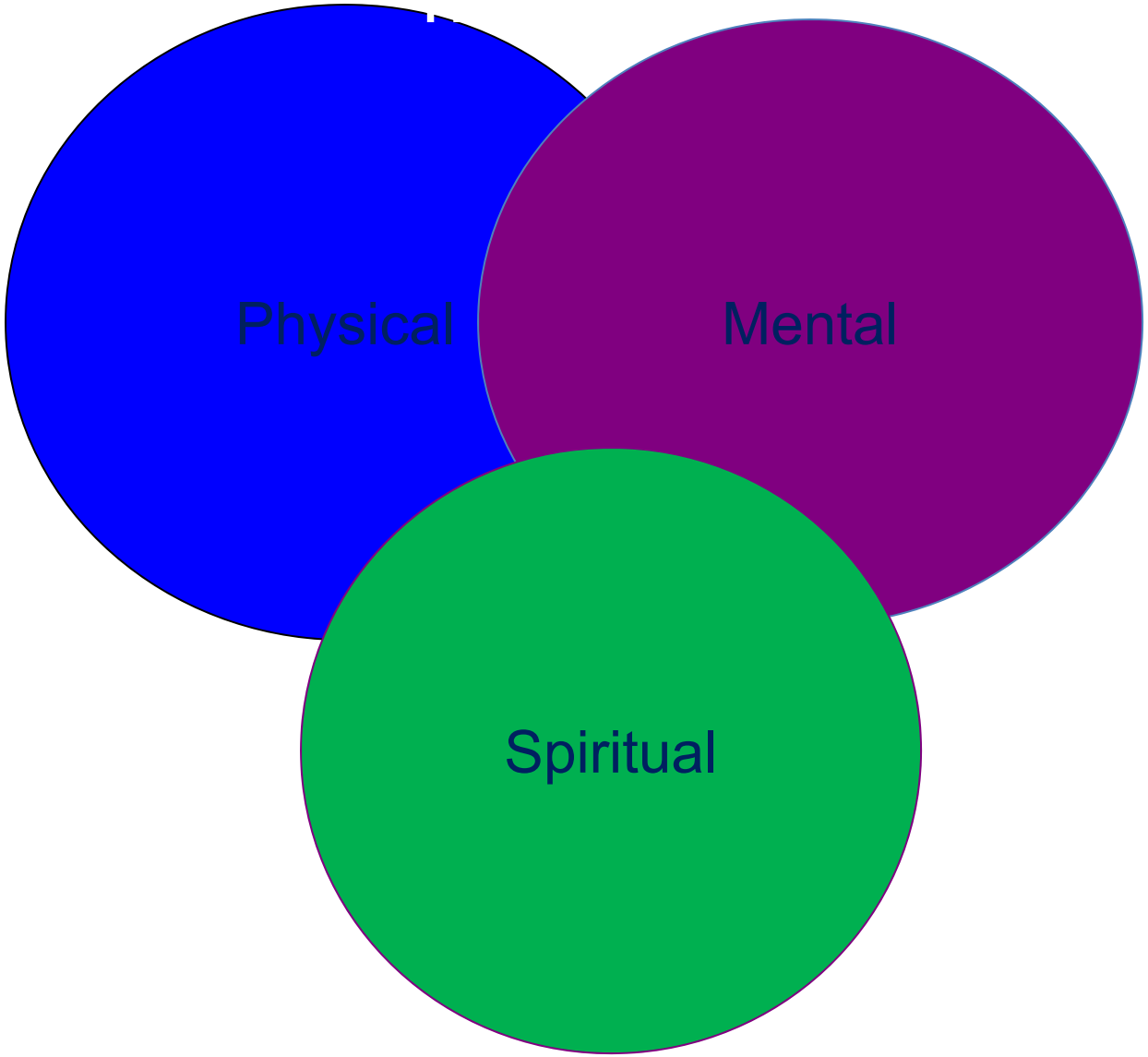
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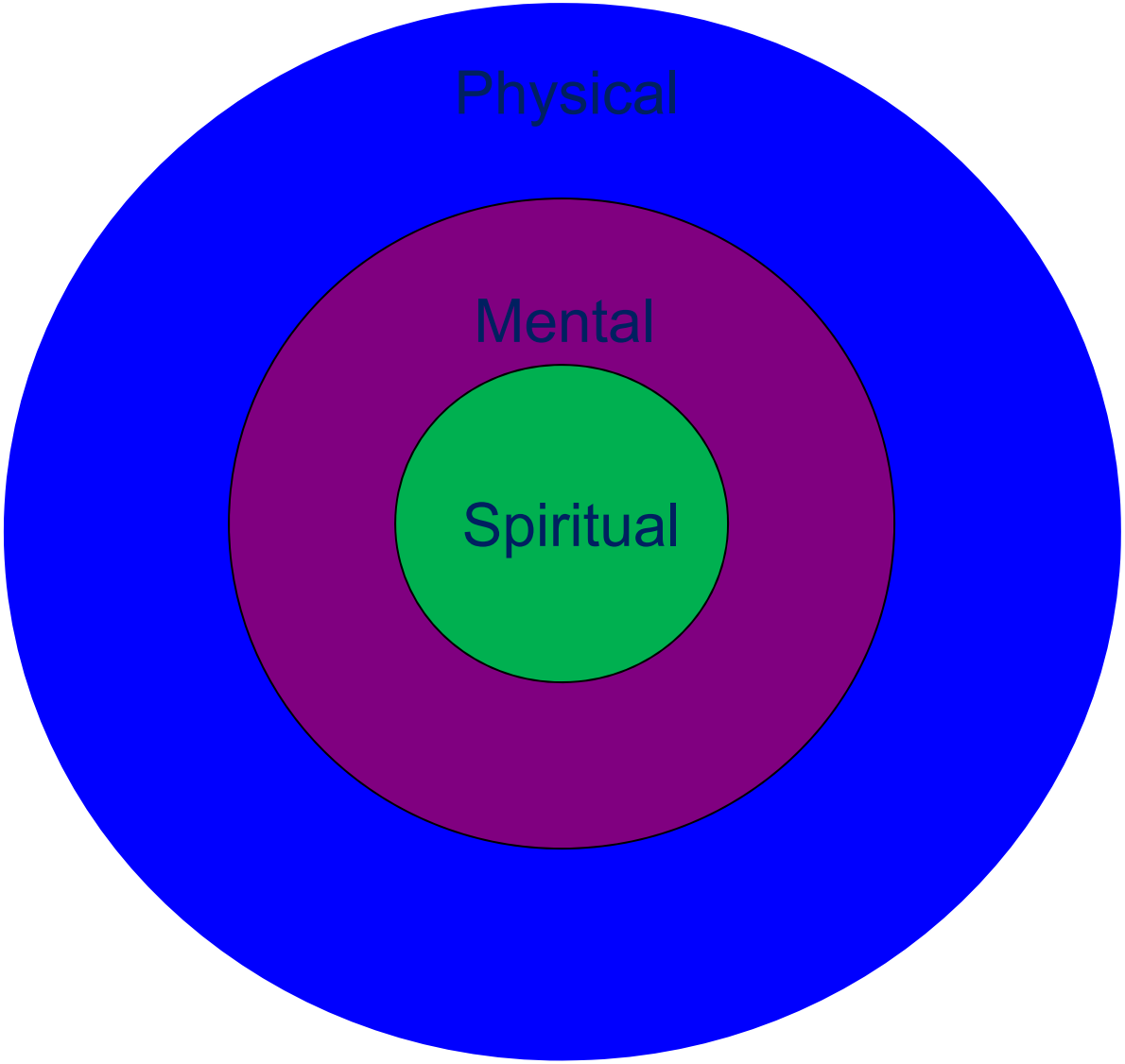

Physical
Mental
Spiritual

"Death is not a strictly medical event, and many patients' and families' most pressing needs are not medical in nature."

Panel comments, *Dying in America: Improving Quality and Honoring Individual preferences Near the End of Life, Institute of Medicine.* http://www.iom.edu/Reports. Released 9/14/14

“The patient’s story is the container for meaning.”

Rachel Naomi Remen

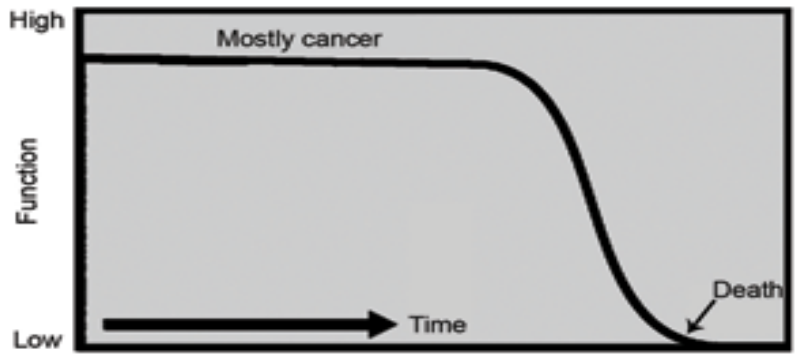
End of Life

- No exact definition
- Multiple trajectories to death
- NIH

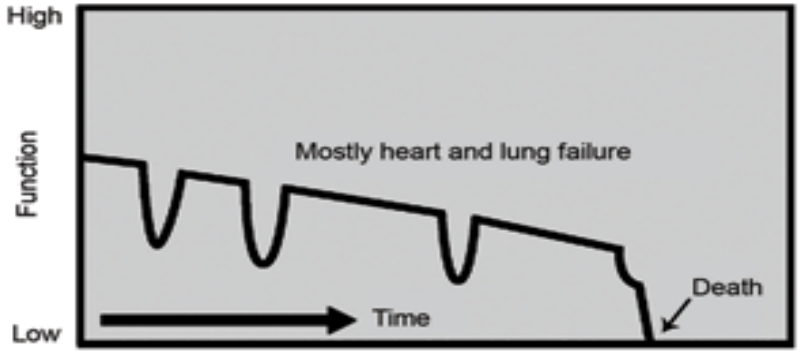
  "People can, in some respects, be considered to be approaching death from the moment they are born."

  National Institutes of Health. National institutes of health state-of-the-science conference statement of improving end-of-life care, http://consensus.nih.gov/2004/2004EndOfLifeCareSOS024html.htm

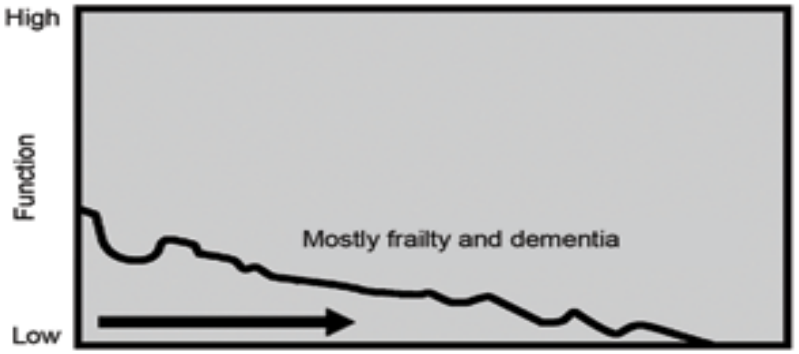
- Practical working definition: life-limiting illness with high likelihood for death within 6-12 months



Short period of evident decline



Long-term limitations with intermittent serious episodes



Prolonged dwindling

Pain

- Location
- Quality
- Quantity
- Setting
- Chronology
- Associated symptoms
- Aggravating and alleviating factors

Intensity

- Awareness 1-2
- Nuisance 3-4
- Aggravation 5-6
- Preoccupying (“All I think about”) 7-8
- Excruciating (“Worst ever”) 9-10

Wong-Baker Facial Pain Scale

No Pain

Worst Pain Ever

Nociceptive Pain

A nociceptor is a nerve fiber preferentially sensitive to a noxious stimulus.

Nociceptive pain is the perception of nociceptive input, usually due to tissue damage.

Rosenquist E, Aronson M, Park L Definition and pathogenesis of chronic pain. UpToDate

Nociceptive Pain

- Somatic
  - Arises from injury to body tissues
  - Well localized but varies in description and experience
- Visceral
  - Arises from viscera mediated by stretch receptors
  - Poorly localized
  - Deep, dull, cramping

Rosenquist E, Aronson M, Park L Definition and pathogenesis of chronic pain. UpToDate

Neuropathic Pain

- Pain caused by a primary nerve injury or dysfunction in the nervous system
- Responsible lesion may be of any type and occur at any location along the sensory transmission pathways
- May be directly related to a life-threatening disease or by a co-morbidity
- May be constant or fluctuating intensity
- May be paroxysmal
- May be spontaneous or provoked by stimulus
- Descriptors may help identify pain as neuropathic

Oxford Textbook of Palliative Medicine, Fourth Edition. Hanks, Cherry, Christakis, et al

Neuropathic Pain Descriptors

- Burning
- Sharp
- Stabbing
- Squeezing
- Shooting
- Pins and needles
- Electric shock
- Cold

Patients often have combination of neuropathic and nociceptive pain (“mixed pain”). Effective pain management should address both types.

Start Simple

- Acetaminophen (Scheduled)
  - Caution
    - Liver disease
    - Pts on warfarin
  - Avoid alcohol with significant scheduled doses
  - Avoid single agent + combination analgesic products

- NSAIDS
  - Caution:
    - Renal disease
    - Hypertension
    - History of ulcers/GI bleeding
    - CHF
    - Advanced liver disease
    - Concurrent anticoagulants

Codeine

- Constipating
- Direct anti-tussive effect
- Metabolic Variation
  - Converted to MORPHINE via CYP2D6 pathway
  - Approximately 7% of Caucasians lack CYP2D6 activity
    - Negligible analgesic effect in these patients
  - “Ultra-rapid metabolizers” (small subset)
    - Potential for extensive conversion to morphine and associated adverse effects
    - Impact may be greatest in pediatric population

Tramadol

- Weak opioid mu-receptor agonist
- Inhibits uptake of serotonin and norepinephrine
  - SNRIs have the same effect
- Fairly rapid pain relief
- Potential to ↓ seizure threshold
- Serotonin syndrome potential
  - SNRI
  - SSRI
- Start with 50 mg PO every 4 hours
- Maximum dose 400 mg/day
- Renal or hepatic impairment requires dose adjustment

Dworkin R, O'Connor A, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clinic Proc* March 2010; 85(3)(suppl):S3-S14

Hydrocodone

- Hydrocodone + acetaminophen
  - Vicodin
  - Lortab
- In 2007, 99% of worldwide hydrocodone consumed in US

  International Narcotics Control Board Report 2008
- Schedule III → Schedule II August 2014
- Converted via CYP2D6 pathway to HYDROMORPHONE
- Zohydro ER approved by FDA in 2014
  - Concerns re: potential for substance abuse
  - FDA review panel recommended 12-2 against approval
  - 30 US states requested that it not be approved in capsule form

Rita Rubin

WebMD Health News

2/27/14

Opioid Equivalents

Drug	Oral/Rectal (mg)	IV/SC (mg)
Morphine	30	10
Oxycodone	20	N/A
Hydromorphone	7.5	1.5
Hydrocodone	30	N/A
Fentanyl	N/A	100 mcg (single dose)

Opiate Adverse Reactions

- Constipation
  - All patients on regular opiates must have a bowel regimen prescribed
    - Docusate has no proven efficacy
    - Stimulant (sennoside) excellent first choice
- Sedation
- Pruritus
- Urinary Retention
- Nausea
- Neuro-excitability
  - Myoclonus
  - Allodynia
    - Ordinarily non-painful stimuli evoke pain

Opiate Principles

- Respiratory depression risk highest in opioid-naïve pts
- Start low and titrate
- Prescribe smaller amounts of short-acting opiate initially
- See patients 1-2 times/wk to adjust dosages until pain is consistently in 2-3/10 range
- Avoid mixing opiates when possible
  - Morphine SR BID + oxycodone Q 4 hours PRN
- One SR opiate (when appropriate) + one IR
- Goal is pain controlled to patient's satisfaction

Initial Opioid Dosing

- Morphine
  - 2.5-5 mg PO q. 2-4 hours PRN
  - 1 mg IV/SC q. hourly PRN
- Hydromorphone
  - 1 mg PO q. 2-4 hours PRN
  - 0.1-0.2 mg IV/SC q. 1 hour PRN
- Fentanyl
  - 12-25 mcg IV/SC q. 1 hour PRN
- Hydrocodone/Acetaminophen
  - 2.5-5 mg PO of the hydrocodone component
  - Hepatic CYP2D6→hydromorphone

Opiates in Renal or Hepatic Dysfunction

Renal

- **Codeine**
  - Do not use
- **Fentanyl**
  - Generally safe
  - May need dose reduction
- **Hydromorphone**
  - 3-glucuronide metabolite can accumulate
- **Methadone**
  - Safe
- **Morphine**
  - Use with caution
  - Active metabolites can accumulate
- **Oxycodone**
  - Caution
  - Parent drug and metabolites can accumulate

Hepatic

- **Codeine**
  - Do not use
- **Fentanyl**
  - Generally safe
  - No dose adjustment necessary (1 dose)
- **Hydromorphone**
  - Caution
  - Reduce dose by 50%
- **Methadone**
  - Do not use long-term
  - May accum in severe hepatic dysfunction
- **Morphine**
  - Use with caution
  - Conversion to inactive metabs may not happen; increase dosing intervals
- **Oxycodone**
  - Use with caution
  - Reduce initial dose 50% and monitor

Groninger H, Vijayan J Pharmacologic management of pain at end of life. *Am Fam Physician* 2014 Jul 1;90 (1):26-32

Methadone

- Racemic mixture of d- and l-isomers
  - d-isomer is not an opiate but a potent N-methyl-D-aspartate antagonist
    - Analgesia in neuropathic pain
- Long plasma half-life (can range from 12 to 150 hours)
- Steady state may take up to 4 weeks to achieve
- Doses should not be changed more frequently than weekly unless the patient is in a closely monitored setting
- Potential for QTc prolongation
  - Watch drug interactions
  - EKG in selected patients
  - Caution in doses > 100 mg per day
- **Should only be used by clinicians familiar with its unique properties**

Brglio K, Abrahm J, Savarese D Pain assessment and management in the last weeks of life. UpToDate

Opiate Stewardship Education

- Sharing opioid medication with others may cause them to have serious reactions or death
- Selling or giving away opioid medication is illegal
- Store in safe AND secure place
  - Children
  - Family members
  - Household visitors
    - Wanted and unwanted
  - Pets
- Proper disposal of unused medication
  - Used fentanyl patch still has enough medication to harm or kill a child

Monograph: ER/LA Opioids: Achieving Safe Use While Improving Patient Care. August 2014 Collaborative for REMS Education, California Academy of Family Physicians

Behaviors Suggestive of Misuse

- Adverse life consequences (e.g., a lost job, relationship problems)
- Current abuse of other substances
- Indications of drug seeking behavior (e.g., seeks early refills)
- Lack of cooperation with opioid treatment plan (e.g., does not follow up with clinical team, refuses to use nonopioid therapies)
- Lack of reliability taking drug (e.g., self-titrates drug, runs out early)
- Loss of control of drug use (e.g., loses prescriptions)

Groninger H, Vijayan J Pharmacologic management of pain at end of life. *Am Fam Physician* 2014 Jul 1;90 (1):26-32

Treatment Options for Neuropathic Pain

- First Line Pharmacologic Choices
  - Tricyclic antidepressants
  - Topical lidocaine
  - Gabapentenoids
    - Gabapentin
    - Pregabalin
  - Selective serotonin noradrenergic reuptake inhibitors (SNRIs)
    - Venlafaxine
    - Duloxetine

Haanpaa M, Gourlay G, et al. Treatment considerations for patients with neuropathic pain and other medical comorbidities. *Mayo Clinic Proc* March 2010; 85(3)(suppl):S15-S25

Tricyclic Antidepressants

- Extensive literature re: efficacy
  - Efficacy questionable in HIV and chemo Rx associated neuropathy
- Inexpensive
- Anti-cholinergic adverse effects may be limiting factor
  - Secondary amine TCA better tolerated (nortriptyline; desimpramine)
- Start with 10 mg @ HS
- Increase by 10-25 mg every 3-7 days→ 75-100 mg
- Avoid or use with caution in elderly
- Avoid or use with great caution in pts with cardiac conduction disturbances or arrhythmia
- Contraindicated after recent MI
- Discuss with pharmacology consultant if any questions

SNRI's

- Duloxetine
  - Efficacy best shown in diabetic neuropathy
    - Evidence for efficacy in chemotherapy induced neuropathy
  - Adequate trial is 4 weeks
  - Nausea is most common adverse effect
  - Start 30 mg daily for 1 week, then increase to 60 mg daily
  - No significant BP or cardiovascular effects

- Venlafaxine
  - Two to for weeks needed to titrate to effective dose (150-225 mg/day)
  - Adequate trial is 4-6 weeks
  - Potential to increase BP
  - Must taper if treatment discontinued
    - Potential for very uncomfortable withdrawal syndrome

Dworkin R, O'Connor A, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clinic Proc* March 2010; 85(3)(suppl):S3-S14

Topical Lidocaine

- Efficacy of 5% lidocaine patch established in RCTs studying different types of NP pain
- Main use is for localized NP
- Helpful for allodynia
- Mild local reactions are main adverse reaction
- No significant systemic reactions or drug interactions
- Lidocaine 5% gel less expensive than patch and has demonstrated efficacy

Dworkin R, O'Connor A, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clinic Proc* March 2010; 85(3)(suppl):S3-S14

Gabapentin

- Binds to voltage-gated calcium channels and inhibits neurotransmitter release
- Dose dependent dizziness and sedation
- Start at low doses (100 mg @ HS for elderly; otherwise 100 mg TID) and titrate gradually
- Dosage reduction needed for renal insufficiency
- Dose Limits:
  - Pain relief
  - Intolerable side effects
  - Maximum dose of 3600 mg daily in divided doses
- Angioedema an uncommon but reported adverse reaction

Pregabalin (Lyrica)

- Same mechanism of action as gabapentin
- Approved FDA 12/31/2004
  - Schedule V
- Starting dose is 50 mg TID
  - Increase to 300 mg/day after 3-7 days
  - Maximum dose is 600 mg/day, but no evidence of added efficacy above 300 mg/day
- Dose reduction needed for renal insufficiency
- Angioedema is a potential adverse reaction
- No clear evidence of superiority of pregabalin over gabapentin

Treatment Options for Neuropathic Pain

- A combination of gabapentin and an opioid has been shown to achieve better analgesia than either drug alone
  - Gilron I, Bailey J, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. *NEJM* 2005;352(13):1324-1334
  - Hanna M, O'Brien C, Wilson MC. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. *Eur J Pain* 2008;12(6):804-813
- Combined gabapentin and nortriptyline therapy has been shown to be more efficacious than either drug given alone for post-herpetic neuralgia
  - Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. *Lancet* 2009;374(9697):1252-1261

Other Potential Adjuvants

- Glucocorticoids (dexamethasone)
- Topicals
  - Lidocaine
  - EMLA
  - Capsaicin
- Alpha-2 agonist
  - Tizanidine
- Selective GABA-B agonist
  - Baclofen
- Ketamine

Naloxone

- Criteria for Use:
  - Depressed mental status: difficult/unable to arouse
  - Shallow respirations or rate less than 8/minute + evidence of inadequate ventilation (e.g. low oxygen saturation, hypotension).
- Stop opioid administration.
- Dilute 0.4 mg naloxone (one amp) with NS to total volume of 10 ml (0.04 mg/mL)
- Prompt pt to breathe deep breaths
- Administer 1 ml IV (0.04 mg) q1min until the patient is responsive.
  - A typical response is noted after 2-4 ml with deeper breathing and greater level of arousal.
- If no response to 0.8 mg (2 amps), consider other causes of sedation and respiratory depression
- Repeated doses of naloxone, or even a continuous naloxone infusion, may be needed.
- Wait for sustained improvement in consciousness before restarting opioids at a lower dose

Dunwoody CJ, Arnold R. Using naloxone. Fast Facts and Concepts #039 End of Life/Palliative Education Resource Center

Opioid Dose Escalation

- For ongoing moderate to severe pain increase opioids doses by 50-100%, irrespective of starting dose
- For ongoing mild to moderate pain increase by 25-50%, irrespective of starting dose
- Dosage escalations of less than 25% generally have no significant efficacy.
- Short-acting oral single-agent opioids can be safely dose escalated every 2 hours (clinician supervised)
- Sustained-release oral opioids can be escalated every 24 hours.

Fast Facts #020 www.eperc.mcw.edu

Opiate Rotation

- Reduce opioid dose by 30-50% to accommodate for unknown cross-tolerance and titrate to goal.
- The wide variation among individuals is multifactorial and poorly understood.
- Incomplete cross-tolerance can lead to greater than anticipated potency in a new opioid, even though same class of analgesic is being used.
- Monitor clinical response and adverse effects.

Kishner S. Opioid equivalents *Medscape*

PCA

- Uses
  - Pain is escalating and not controlled with oral regimen
  - Persistent vomiting
  - Transition after procedures
  - More precise determination of opiate need
- Somnolence occurs before respiratory depression
- Basal infusion can be added once PRN use is assessed
- Typical starting dose in opiate naive pt:
  - Hydromorphone 0.1 mg IV with 12 min lockout
  - Morphine 1 mg IV with 12 min lockout
  - Fentanyl 12 mcg with 12 min lockout
- Patient or nurse activated, NOT FAMILY!

PCA Conversion

- 64 yo male, with metastatic SCC of lung with metastasis to liver, bone, and subcutaneous tissues has been on MS Contin 30 mg PO BID + 5 mg oral morphine every 2 hours PRN for breakthrough pain. In the last 24 hours he has used 5 doses of oral morphine, and presents to ED with vomiting and persistent pain that he rates 8/10. He has normal renal function and is alert. You decide to rotate to hydromorphone using a PCA.
- Calculate total OME
  - 30 + 30 + (5 x 5) = 85 mg in 24 hour = 3.5 mg per hour
- Convert to equivalent IV HYDROMORPHONE
  - 3.5 ÷ 20 = 0.175 mg x 0.7 = 0.123 mg→ 0.1 mg IV hydromorphone per hour
- PCA dose 0.1 mg hydromorphone with 12 min lockout
- Reassess pain control in 6-8 hours and adjust dose

Pain Crisis Management

- Morphine 2 mg IV initial dose
  - If no response in 10 minutes repeat 2 mg dose
  - If no response in 10 minutes, give 5 mg Q 10 min x 2 doses
  - If no response give 10 mg Q 10 minutes until pain controlled
  - Once a dose is starting to relieve pain, continue with that same bolus dose every 10 minutes until pain is 2-3/10.
  - ONCE PAIN CONTROLLED: calculate total amount of opiate used
    - Give this amount over 24 hours as basal infusion with bolus dose the same mg as used for hourly infusion
- Example:
  - 2 mg + 2 mg + 5 mg + 5 mg + 10 mg morphine controls pain
  - 24 mg ÷ 24 = 1 mg/hour basal morphine infusion
  - PCA (or NCA) bolus 1 mg with 12 min lockout
  - If pain starts to escalate, ↑ infusion + bolus by 100% & reassess

IV Lidocaine in Opioid-Resistant Pain

- Randomized, double-blinded, placebo-controlled, cross over study of 50 consecutive cancer patients not responding to maximally tolerated morphine dose
- Primary end-points: Magnitude of pain relief and durability of response
- Equal volumes of NS or Lidocaine
- Lidocaine
  - 2 mg/kg bolus
  - 2 mg/kg infusion over one hour
- ECG monitoring during bolus and for 2 hrs following infusion
- Non-invasive BP and respiratory rate monitoring every 10 min

Sharma S, Rajagopal M, Palat G, Singh C, et al. A phase II pilot study to evaluate use of intravenous lidocaine for opoid-refractory pain in cancer patients. *Journal of Pain and Symptom Management* Jan 2009;(37)1:85-93

IV Lidocaine in Opioid-Resistant Pain

- Pain Types
  - 26 (52%) Mixed
  - 15 (30%) Nociceptive
  - 9 (18%) Neuropathic

Sharma S, Rajagopal M, Palat G, Singh C, et al. A phase II pilot study to evaluate use of intravenous lidocaine for opoid-refractory pain in cancer patients. *Journal of Pain and Symptom Management* Jan 2009;(37)1:85-93

IV Lidocaine in Opioid-Resistant Pain

	Lidocaine	Placebo
Mean time to maximal effect	40 min	75 min
Mean duration of pain relief	9.34 days	3.82 days
% of patients reporting subjective decrease in analgesic requirements in 14 day f/u observation period	64%	30%

Sharma S, Rajagopal M, Palat G, Singh C, et al A phase II pilot study to evaluate use of intravenous lidocaine for opoid-refractory pain in cancer patients. *Journal of Pain and Symptom Management* Jan 2009;(37)1:85-93

Summary

- Pain has sensory and emotional elements
- Pain in EOL scenarios often has nociceptive and neuropathic aspects to consider
- Effective EOL pain management utilizes opiate and non-opiate medication
- Escalating pain should be anticipated in EOL care
- Escalating pain can be effectively managed by family physicians